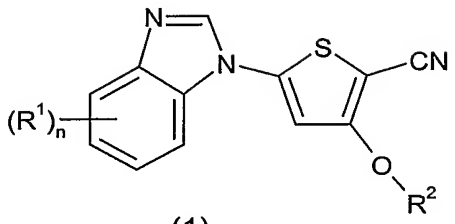
CLAIMS

We claim:

1. A compound of Formula (I):



(1)

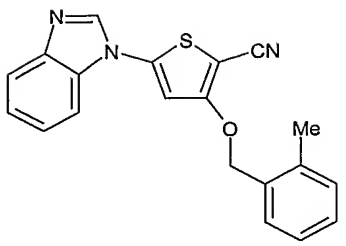
wherein

n is 0, 1, 2, 3, or 4;
Each R^1 which may be the same or different, independently represents H, halogen or a group $(X)_a(Y)_bZ$;
X represents -O- or -CONH-;
a is 0 or 1;
Y represents -C_{1-6} alkylene-
b is 0 or 1;
Z represents hydroxy, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{5-7} heterocyclyl, C_{1-6} alkoxyalkyl, C_{1-6} haloalkoxyalkyl;

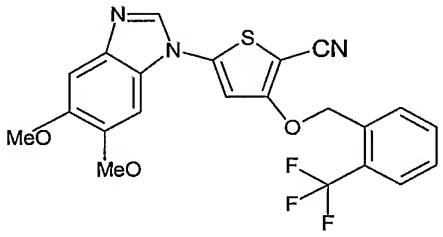
R^2 represents a group $-(X^1)_C(Y^1)_dZ^1$

Wherein X^1 represents –C_{1-12} alkylene-;
c is 0 or 1;
Y^1 represents –O-;
d is 0 or 1;
Z^1 represents H, aryl or heteroaryl each of which contains 5 - 14 ring atoms, C_{5-7} heterocyclyl, C_{5-7} cycloalkyl, C_{5-7} cycloalkenyl, (each of which aryl, heteroaryl, heterocyclyl, cycloalkyl, cycloalkenyl may be optionally substituted by one or more substituents independently selected from C_{1-6} alkyl, C_{1-6} haloalkyl, halogen, C_{1-6} alkoxy, C_{1-6} haloalkoxy, SO_2R^3, C_{1-6} hydroxyalkyl).
R^3 represents H or C_{1-6} alkyl;
or pharmaceutically acceptable salts, solvates or physiologically functional derivatives thereof with the proviso that the compound is not:

5-(1*H*-benzimidazol-1-yl)-3-{(2-methylphenyl)oxy]thiophene-2-carbonitrile



or 5-(5,6-bismethoxy-1*H*-benzimidazol-1-yl)-3-{(2-trifluoromethyl)phenyl]oxy}thiophene-2-carbonitrile



2. A compound according to claim 1 wherein n is 1 or 2.

3. A compound according to claim 1 wherein n is 2.

4. A compound according to claim 3 wherein one R^1 is – OCH_3.

5. A compound according to claim 3 wherein both R^1 are –OCH_3.

6. A compound according to claim 6 wherein each R^1 is –OCH_3 on position 5 and 6 of the ring.

7. A compound according to claims 1-7 wherein c is 1.

8. A compound according to claims 1-7 wherein X^1 is C_{1-6}alkenyl.

9. A compound according to claims 1-8 wherein Z^1 is aryl or heteroaryl each of which is optionally substituted by one or more substituents independently selected from halogen, CF_3 CH_2OH, SO_2CH_3, CH_3, OCH_3.

10. A compound according to claim 1, selected from:

5-[5,6-bis(methyloxy)-1H-benzimidazol-1-yl]-3-({[4-(hydroxymethyl)phenyl]methyl}oxy)-2-thiophenecarbonitrile
5-[5,6-bis(methyloxy)-*1H*-benzimidazol-1-yl]-3-{[(1*R*)-1-(2-chlorophenyl)ethyl]oxy}-2-thiophenecarbonitrile
5-(*1H*-benzimidazol-1-yl)-3-[(phenylmethyl)oxy]-2-thiophenecarbonitrile
5-[5,6-bis(methyloxy)-*1H*-benzimidazol-1-yl]-3-{[(1-methyl-*1H*-1,2,3-benzotriazol-6-yl)methyl]oxy}-2-thiophenecarbonitrile)
5-(6-(methyloxy)-5-{[2-(4-morpholinyl)ethyl]oxy}-*1H*-benzimidazol-1-yl)-3-({[2-(trifluoromethyl)phenyl]methyl}oxy)-2-thiophenecarbonitrile
5-[5,6-bis(methyloxy)-*1H*-benzimidazol-1-yl]-3-{[(2,5-difluorophenyl)methyl]oxy}-2-thiophenecarbonitrile
5-[5,6-bis(methyloxy)-*1H*-benzimidazol-1-yl]-3-({[2-(methylsulfonyl)phenyl]methyl}oxy)-2-thiophenecarbonitrile
5-(5-chloro-*1H*-benzimidazol-1-yl)-3-[(phenylmethyl)oxy]-2-thiophenecarbonitrile
5-[5,6-bis(methyloxy)-*1H*-benzimidazol-1-yl]-3-{[(2,6-difluorophenyl)methyl]oxy}-2-thiophenecarbonitrile
5-[5-[(3-hydroxypropyl)oxy]-6-(methyloxy)-*1H*-benzimidazol-1-yl]-3-({[2-(trifluoromethyl)phenyl]methyl}oxy)-2-thiophene-carbonitrile
5-[5,6-bis(methyloxy)-*1H*-benzimidazol-1-yl]-3-{[(3-bromo-4-pyridinyl)methyl]oxy}-2-thiophenecarbonitrile
5-[5,6-bis(methyloxy)-*1H*-benzimidazol-1-yl]-3-[(cyclohexylmethyl)oxy]-2-thiophenecarbonitrile
1-[5-cyano-4-({[2-(trifluoromethyl)phenyl]methyl}oxy)-2-thienyl]-*N*-[2-(4-morpholinyl)ethyl]-*1H*-benzimidazole-5-carboxamide
5-[5,6-bis(methyloxy)-*1H*-benzimidazol-1-yl]-3-({(1*R*)-1-[2-(trifluoromethyl)phenyl]ethyl}oxy)-2-thiophenecarbonitrile
5-[5,6-bis(methyloxy)-*1H*-benzimidazol-1-yl]-3-[(2-phenylethyl)oxy]-2-thiophenecarbonitrile
5-[5,6-bis(methyloxy)-*1H*-benzimidazol-1-yl]-3-[({2-[(trifluoromethyl)oxy]phenyl}methyl)oxy]-2-thiophenecarbonitrile
5-[5,6-bis(methyloxy)-*1H*-benzimidazol-1-yl]-3-({[2-(methyloxy)phenyl]methyl}oxy)-2-thiophenecarbonitrile
5-[5,6-bis(methyloxy)-*1H*-benzimidazol-1-yl]-3-{[2-(4-morpholinyl)ethyl]oxy}-2-thiophenecarbonitrile
5-[5,6-bis(methyloxy)-*1H*-benzimidazol-1-yl]-3-{[2-(2-oxo-1-pyrrolidinyl)ethyl]oxy}-2-thiophenecarbonitrile
5-[5,6-bis(methyloxy)-*1H*-benzimidazol-1-yl]-3-[(tetrahydro-2-furanylmethyl)oxy]-2-thiophenecarbonitrile
5-[5,6-bis(methyloxy)-*1H*-benzimidazol-1-yl]-3-[(tetrahydro-2*H*-pyran-2-ylmethyl)oxy]-2-

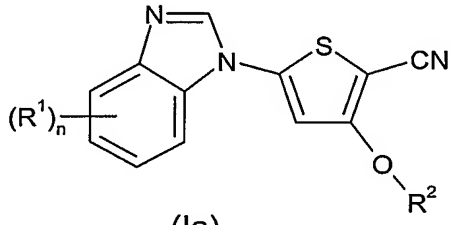
thiophenecarbonitrile
5-[5,6-bis(methyloxy)-*1H*-benzimidazol-1-yl]-3-{[2-(phenyloxy)ethyl]oxy}-2-thiophenecarbonitrile
5-[5,6-bis(methyloxy)-*1H*-benzimidazol-1-yl]-3-{[(1*S*)-1-(2-chlorophenyl)butyl]oxy}-2-thiophenecarbonitrile
5-[5,6-bis(methyloxy)-*1H*-benzimidazol-1-yl]-3-[(3-thienylmethyl)oxy]-2-thiophenecarbonitrile
5-[5,6-bis(methyloxy)-*1H*-benzimidazol-1-yl]-3-[(2-thienylmethyl)oxy]-2-thiophenecarbonitrile
5-[5,6-bis(methyloxy)-*1H*-benzimidazol-1-yl]-3-{[(1*R*)-1-methylpropyl]oxy}-2-thiophenecarbonitrile

or a salt, solvate, or physiologically functional derivative thereof.

11. A pharmaceutical composition, comprising: a therapeutically effective amount of a compound as claimed in any one of claims 1 or 2, or a salt, solvate, or a physiologically functional derivative thereof and one or more of pharmaceutically acceptable carriers, diluents and excipients.

12. A compound as claimed in any of claims 1 or 2, or a salt, solvate, or a physiologically functional derivative thereof for use in therapy.

13. A method of treating a disorder in a mammal, said disorder being mediated by at least one of inappropriate IKK3 activity, comprising: administering to said mammal a therapeutically effective amount of a compound of Formula (Ia)



(Ia)

wherein

n is 0, 1, 2, 3, or 4;
Each R^1 which may be the same or different, independently represents H, halogen or a group $(X)_a(Y)_bZ$;
X represents –0- or –CONH-;
a is 0 or 1;
Y represents -C_{1-6} alkylene-
b is 0 or 1;

Z represents hydroxy, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{5-7} heterocyclyl, C_{1-6} alkoxyalkyl, C_{1-6} haloalkoxyalkyl;
R^2 represents a group $-(X^1)_c(Y^1)_dZ^1$;

Wherein X^1 represents $-C_{1-6}$ alkylene-;
c is 0 or 1;
Y^1 represents –O-;
d is 0 or 1;
Z^1 represents H, aryl or heteroaryl each of which contains 5 - 14 ring members, C_{5-7} heterocyclyl, C_{5-7} cycloalkyl, C_{5-7} cycloalkenyl (each of which aryl, heteroaryl, heterocyclyl, cycloalkyl, cycloalkeny may be optionally substituted by one or more substituents independently selected from C_{1-6} alkyl, C_{1-6} haloalkyl, halogen, C_{1-6} alkoxy, C_{1-6} haloalkoxy, SO_2R^3, C_{1-6} hydroxyalkyl)
R^3 represents H or C_{1-6} alkyl;
or pharmaceutically acceptable salts, solvates or physiologically functional derivatives thereof.

14. A method according to claim 5 wherein the disorder mediated by inappropriate IKK3 activity is inflammatory bowel disease, asthma and COPD (chronic obstructive pulmonary disease); osteoarthritis, osteoporosis and fibrotic diseases; dermatosis, including psoriasis, atopic dermatitis and ultraviolet radiation (UV)-induced skin damage; autoimmune diseases including systemic lupus eythematosus, multiple sclerosis, psoriatic arthritis, alkylosing spondylitis, tissue and organ rejection, Alzheimer's disease, stroke, atherosclerosis, restonosis, diabetes, glomerulonephritis, cancer, including Hodgkins disease, cachexia, inflammation associated with infection and certain viral infections, including acquired immune deficiency syndrome (AIDS), adult respiratory distress syndrome, and Ataxia Telangiestasia.

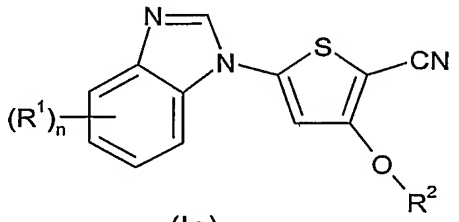
15. A method according to claim 13 or 14 wherein the compound of Formula (Ia) is selected from:

5-[5,6-bis(methyloxy)-1H-benzimidazol-1-yl]-3-({[4-(hydroxymethyl)phenyl]methyl}oxy)-2-thiophenecarbonitrile
5-[5,6-bis(methyloxy)-*1H*-benzimidazol-1-yl]-3-{[(1*R*)-1-(2-chlorophenyl)ethyl]oxy}-2-thiophenecarbonitrile
5-(*1H*-benzimidazol-1-yl)-3-{[(2-methylphenyl)methyl]oxy}-2-thiophenecarbonitrile
5-(*1H*-benzimidazol-1-yl)-3-[(phenylmethyl)oxy]-2-thiophenecarbonitrile
5-[5,6-bis(methyloxy)-*1H*-benzimidazol-1-yl]-3-{[(1-methyl-*1H*-1,2,3-benzotriazol-6-yl)methyl]oxy}-2-thiophenecarbonitrile)
5-(6-(methyloxy)-5-{[2-(4-morpholinyl)ethyl]oxy}-*1H*-benzimidazol-1-yl)-3-({[2-(trifluoromethyl)phenyl]methyl}oxy)-2-thiophenecarbonitrile
5-[5,6-bis(methyloxy)-*1H*-benzimidazol-1-yl]-3-{[(2,5-difluorophenyl)methyl]oxy}-2-

thiophenecarbonitrile
5-[5,6-bis(methyloxy)-*1H*-benzimidazol-1-yl]-3-({[2-(trifluoromethyl)phenyl]methyl}oxy)-2-thiophenecarbonitrile
5-[5,6-bis(methyloxy)-*1H*-benzimidazol-1-yl]-3-({[2-(methylsulfonyl)phenyl]methyl}oxy)-2-thiophenecarbonitrile
5-(5-chloro-*1H*-benzimidazol-1-yl)-3-[(phenylmethyl)oxy]-2-thiophenecarbonitrile
5-[5,6-bis(methyloxy)-*1H*-benzimidazol-1-yl]-3-{[(2,6-difluorophenyl)methyl]oxy}-2-thiophenecarbonitrile
5-[5-[(3-hydroxypropyl)oxy]-6-(methyloxy)-*1H*-benzimidazol-1-yl]-3-({[2-(trifluoromethyl)phenyl]methyl}oxy)-2-thiophene-carbonitrile
5-[5,6-bis(methyloxy)-*1H*-benzimidazol-1-yl]-3-{[(3-bromo-4-pyridinyl)methyl]oxy}-2-thiophenecarbonitrile
5-[5,6-bis(methyloxy)-*1H*-benzimidazol-1-yl]-3-[(cyclohexylmethyl)oxy]-2-thiophenecarbonitrile
1-[5-cyano-4-({[2-(trifluoromethyl)phenyl]methyl}oxy)-2-thienyl]-*N*-[2-(4-morpholinyl)ethyl]-*1H*-benzimidazole-5-carboxamide
5-[5,6-bis(methyloxy)-*1H*-benzimidazol-1-yl]-3-({(1*R*)-1-[2-(trifluoromethyl)phenyl]ethyl}oxy)-2-thiophenecarbonitrile
5-[5,6-bis(methyloxy)-*1H*-benzimidazol-1-yl]-3-[(2-phenylethyl)oxy]-2-thiophenecarbonitrile
5-[5,6-bis(methyloxy)-*1H*-benzimidazol-1-yl]-3-[({2-[(trifluoromethyl)oxy]phenyl}methyl)oxy]-2-thiophenecarbonitrile
5-[5,6-bis(methyloxy)-*1H*-benzimidazol-1-yl]-3-({[2-(methyloxy)phenyl]methyl}oxy)-2-thiophenecarbonitrile
5-[5,6-bis(methyloxy)-*1H*-benzimidazol-1-yl]-3-{[2-(4-morpholinyl)ethyl]oxy}-2-thiophenecarbonitrile
5-[5,6-bis(methyloxy)-*1H*-benzimidazol-1-yl]-3-{[2-(2-oxo-1-pyrrolidinyl)ethyl]oxy}-2-thiophenecarbonitrile
5-[5,6-bis(methyloxy)-*1H*-benzimidazol-1-yl]-3-[(tetrahydro-2-furanylmethyl)oxy]-2-thiophenecarbonitrile
5-[5,6-bis(methyloxy)-*1H*-benzimidazol-1-yl]-3-[(tetrahydro-2*H*-pyran-2-ylmethyl)oxy]-2-thiophenecarbonitrile
5-[5,6-bis(methyloxy)-*1H*-benzimidazol-1-yl]-3-{[2-(phenyloxy)ethyl]oxy}-2-thiophenecarbonitrile
5-[5,6-bis(methyloxy)-*1H*-benzimidazol-1-yl]-3-{[(1*S*)-1-(2-chlorophenyl)butyl]oxy}-2-thiophenecarbonitrile
5-[5,6-bis(methyloxy)-*1H*-benzimidazol-1-yl]-3-[(3-thienylmethyl)oxy]-2-thiophenecarbonitrile
5-[5,6-bis(methyloxy)-*1H*-benzimidazol-1-yl]-3-[(2-thienylmethyl)oxy]-2-thiophenecarbonitrile
5-[5,6-bis(methyloxy)-*1H*-benzimidazol-1-yl]-3-{[(1*R*)-1-methylpropyl]oxy}-2-thiophenecarbonitrile

or a salt, solvate or physiologically functional derivative thereof.

16. Use of a compound of Formula (Ia),



(Ia)

wherein

n is 0, 1, 2, 3, or 4;
Each R^1 which may be the same or different, independently represents H, halogen or a group $(X)_a(Y)_bZ$;
X represents –0- or –CONH-;
a is 0 or 1;
Y represents -C_{1-6} alkylene-
b is 0 or 1;
Z represents hydroxy, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{5-7} heterocyclyl, C_{1-6} alkoxyalkyl, C_{1-6} haloalkoxyalkyl;
R^2 represents a group $-(X^1)_C(Y^1)_dZ^1$;

Wherein X^1 represents –C_{1-6} alkylene-;
c is 0 or 1;
Y^1 represents –O-;
d is 0 or 1;
Z^1 represents H, aryl or heteroaryl each of which contains 5 - 14 ring members, C_{5-7} heterocyclyl, C_{5-7} cycloalkyl, C_{5-7} cycloalkenyl (each of which aryl, heteroaryl, heterocyclyl, cycloalkyl, cycloalkeny may be optionally substituted by one or more substituents independently selected from C_{1-6} alkyl, C_{1-6} haloalkyl, halogen, C_{1-6} alkoxy, C_{1-6} haloalkoxy, SO_2R^3, C_{1-6} hydroxyalkyl)
R^3 represents H or C_{1-6} alkyl;
or pharmaceutically acceptable salts, solvates or physiologically functional derivatives thereof.in the preparation of a medicament for use in the treatment of a disorder mediated by inappropriate IKK3 activity.

17. Use according to claim 16 wherein disorder mediated by inappropriate IKK3 activity is inflammatory bowel disease, asthma and COPD (chronic obstructive pulmonary disease); osteoarthritis, osteoporosis and fibrotic diseases; dermatosis, including

psoriasis, atopic dermatitis and ultraviolet radiation (UV)-induced skin damage; autoimmune diseases including systemic lupus eythematosus, multiple sclerosis, psoriatic arthritis, alkylosing spondylitis, tissue and organ rejection, Alzheimer's disease, stroke, atherosclerosis, restonosis, diabetes, glomerulonephritis, cancer, including Hodgkins disease, cachexia, inflammation associated with infection and certain viral infections, including acquired immune deficiency syndrome (AIDS), adult respiratory distress syndrome, and Ataxia Telangiestasia.

18. Use according to claim 16 or 17 where the compound of Formula (Ia) is selected from:

5-[5,6-bis(methyloxy)-1H-benzimidazol-1-yl]-3-({[4-(hydroxymethyl)phenyl]methyl}oxy)-2-thiophenecarbonitrile
5-[5,6-bis(methyloxy)-*1H*-benzimidazol-1-yl]-3-{[(1*R*)-1-(2-chlorophenyl)ethyl]oxy}-2-thiophenecarbonitrile
5-(*1H*-benzimidazol-1-yl)-3-{[(2-methylphenyl)methyl]oxy}-2-thiophenecarbonitrile
5-(*1H*-benzimidazol-1-yl)-3-[(phenylmethyl)oxy]-2-thiophenecarbonitrile
5-[5,6-bis(methyloxy)-*1H*-benzimidazol-1-yl]-3-{[(1-methyl-*1H*-1,2,3-benzotriazol-6-yl)methyl]oxy}-2-thiophenecarbonitrile)
5-(6-(methyloxy)-5-{[2-(4-morpholinyl)ethyl]oxy}-*1H*-benzimidazol-1-yl)-3-({[2-(trifluoromethyl)phenyl]methyl}oxy)-2-thiophenecarbonitrile
5-[5,6-bis(methyloxy)-*1H*-benzimidazol-1-yl]-3-{[(2,5-difluorophenyl)methyl]oxy}-2-thiophenecarbonitrile
5-[5,6-bis(methyloxy)-*1H*-benzimidazol-1-yl]-3-({[2-(trifluoromethyl)phenyl]methyl}oxy)-2-thiophenecarbonitrile
5-[5,6-bis(methyloxy)-*1H*-benzimidazol-1-yl]-3-({[2-(methylsulfonyl)phenyl]methyl}oxy)-2-thiophenecarbonitrile
5-(5-chloro-*1H*-benzimidazol-1-yl)-3-[(phenylmethyl)oxy]-2-thiophenecarbonitrile
5-[5,6-bis(methyloxy)-*1H*-benzimidazol-1-yl]-3-{[(2,6-difluorophenyl)methyl]oxy}-2-thiophenecarbonitrile
5-[5-[(3-hydroxypropyl)oxy]-6-(methyloxy)-*1H*-benzimidazol-1-yl]-3-({[2-(trifluoromethyl)phenyl]methyl}oxy)-2-thiophene-carbonitrile
5-[5,6-bis(methyloxy)-*1H*-benzimidazol-1-yl]-3-{[(3-bromo-4-pyridinyl)methyl]oxy}-2-thiophenecarbonitrile
5-[5,6-bis(methyloxy)-*1H*-benzimidazol-1-yl]-3-[(cyclohexylmethyl)oxy]-2-thiophenecarbonitrile
1-[5-cyano-4-({[2-(trifluoromethyl)phenyl]methyl}oxy)-2-thienyl]-*N*-[2-(4-morpholinyl)ethyl]-*1H*-benzimidazole-5-carboxamide
5-[5,6-bis(methyloxy)-*1H*-benzimidazol-1-yl]-3-({(1*R*)-1-[2-(trifluoromethyl)phenyl]ethyl}oxy)-2-thiophenecarbonitrile
5-[5,6-bis(methyloxy)-*1H*-benzimidazol-1-yl]-3-[(2-phenylethyl)oxy]-2-thiophenecarbonitrile

5-[5,6-bis(methyloxy)-*1H*-benzimidazol-1-yl]-3-[({2-[(trifluoromethyl)oxy]phenyl}methyl)oxy]-2-thiophenecarbonitrile
5-[5,6-bis(methyloxy)-*1H*-benzimidazol-1-yl]-3-({[2-(methyloxy)phenyl]methyl}oxy)-2-thiophenecarbonitrile
5-[5,6-bis(methyloxy)-*1H*-benzimidazol-1-yl]-3-{[2-(4-morpholinyl)ethyl]oxy}-2-thiophenecarbonitrile
5-[5,6-bis(methyloxy)-*1H*-benzimidazol-1-yl]-3-{[2-(2-oxo-1-pyrrolidinyl)ethyl]oxy}-2-thiophenecarbonitrile
5-[5,6-bis(methyloxy)-*1H*-benzimidazol-1-yl]-3-[(tetrahydro-2-furanylmethyl)oxy]-2-thiophenecarbonitrile
5-[5,6-bis(methyloxy)-*1H*-benzimidazol-1-yl]-3-[(tetrahydro-2*H*-pyran-2-ylmethyl)oxy]-2-thiophenecarbonitrile
5-[5,6-bis(methyloxy)-*1H*-benzimidazol-1-yl]-3-{[2-(phenyloxy)ethyl]oxy}-2-thiophenecarbonitrile
5-[5,6-bis(methyloxy)-*1H*-benzimidazol-1-yl]-3-{[(1*S*)-1-(2-chlorophenyl)butyl]oxy}-2-thiophenecarbonitrile
5-[5,6-bis(methyloxy)-*1H*-benzimidazol-1-yl]-3-[(3-thienylmethyl)oxy]-2-thiophenecarbonitrile
5-[5,6-bis(methyloxy)-*1H*-benzimidazol-1-yl]-3-[(2-thienylmethyl)oxy]-2-thiophenecarbonitrile
5-[5,6-bis(methyloxy)-*1H*-benzimidazol-1-yl]-3-{[(1*R*)-1-methylpropyl]oxy}-2-thiophenecarbonitrile

or a salt, solvate or physiologically functional derivative thereof.